

Population PK/PD modeling of tumor growth inhibition in tumor bearing mice : *a translational strategy to predict clinical efficacy ?*

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Status and Problem

Assessing the efficacy of candidate anticancer agents in the preclinical setting is typically carried out by evaluating the inhibition of the growth of tumor xenografts, (human tumor cell lines engrafted into mice), however, the predictive value of such experimental models have been challenged. Another challenge has been the translation of the minimal exposure required for antitumor activity in experimental models, into optimal administration modalities (pharmacologically active dose & schedule) in the clinical setting. The aim of this study was to develop a translational oriented population PK/PD model for tumor growth inhibition (TGI) induced by the new antibody-drug-conjugate (ADC) SARx, when administered to SCID mice bearing a more relevant tumor model, a colon patient-derived xenograft (PDX), and then to apply the translational strategy to help selecting appropriate dosing schedule for first in human study.

Pharmacometric Approach

1) Population PK modeling in mice:

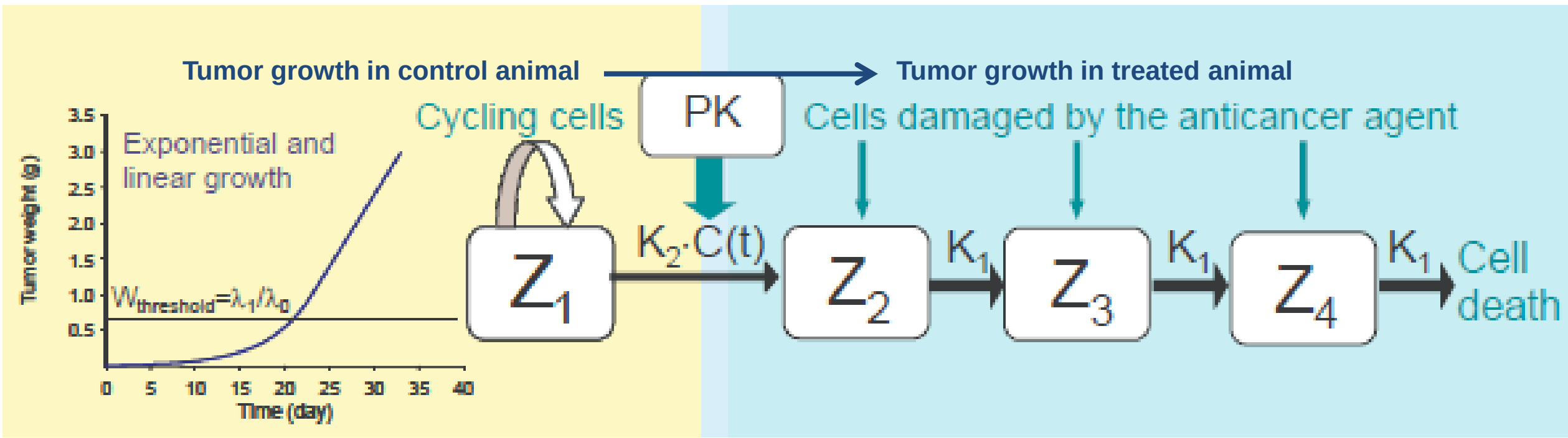
286 PK observations in 113 treated mice from Study 1 (Mice bearing advanced colon PDX receiving **single IV bolus** of SARx 0.75, 2.5, 5 mg/kg or vehicle).

2) Tumor growth modeling (Simeoni) in mice:

- a. PK/PD modeling of **Study 1 alone** (470 Tumor volumes)
- b. Design of **Study 2 using simulations** (42 mice bearing advanced colon PDX receiving **single or repeated IV bolus** of SARx from 5 to 20 mg/kg or vehicle, using the following schedules: every 2 weeks, weekly and twice weekly [No PK data])
- c. PK/PD modeling refinement using data from both studies (470 tumor volumes from Study 1 + 673 tumor volumes [of which 327 below limit of palpation] from Study 2)

3) Population PK in monkey

78 PK observations from TK1 (Single IV infusion at 5, 10 and 15 mg/kg, 4 monkeys per dose group) + 158 PK observations from TK2 (Weekly repeated IV infusion at 2, 5 and 10 mg/kg for 3 weeks, 4 monkeys per dose group)
PK in monkey were used to predict PK in human based on allometry.



Simeoni Model's parameters:

K2: drug potency
CT: threshold conc. for tumor eradication ($CT = \lambda_0 / K_2$)

4) Clinical translation

The predicted PK in human and the established CT were used to predict minimum active dose in human
The analyses were performed using the Stochastic Approximation Expectation Maximization algorithm for nonlinear mixed-effects models implemented in MONOLIX (version 4.1.3 and 4.2.2).

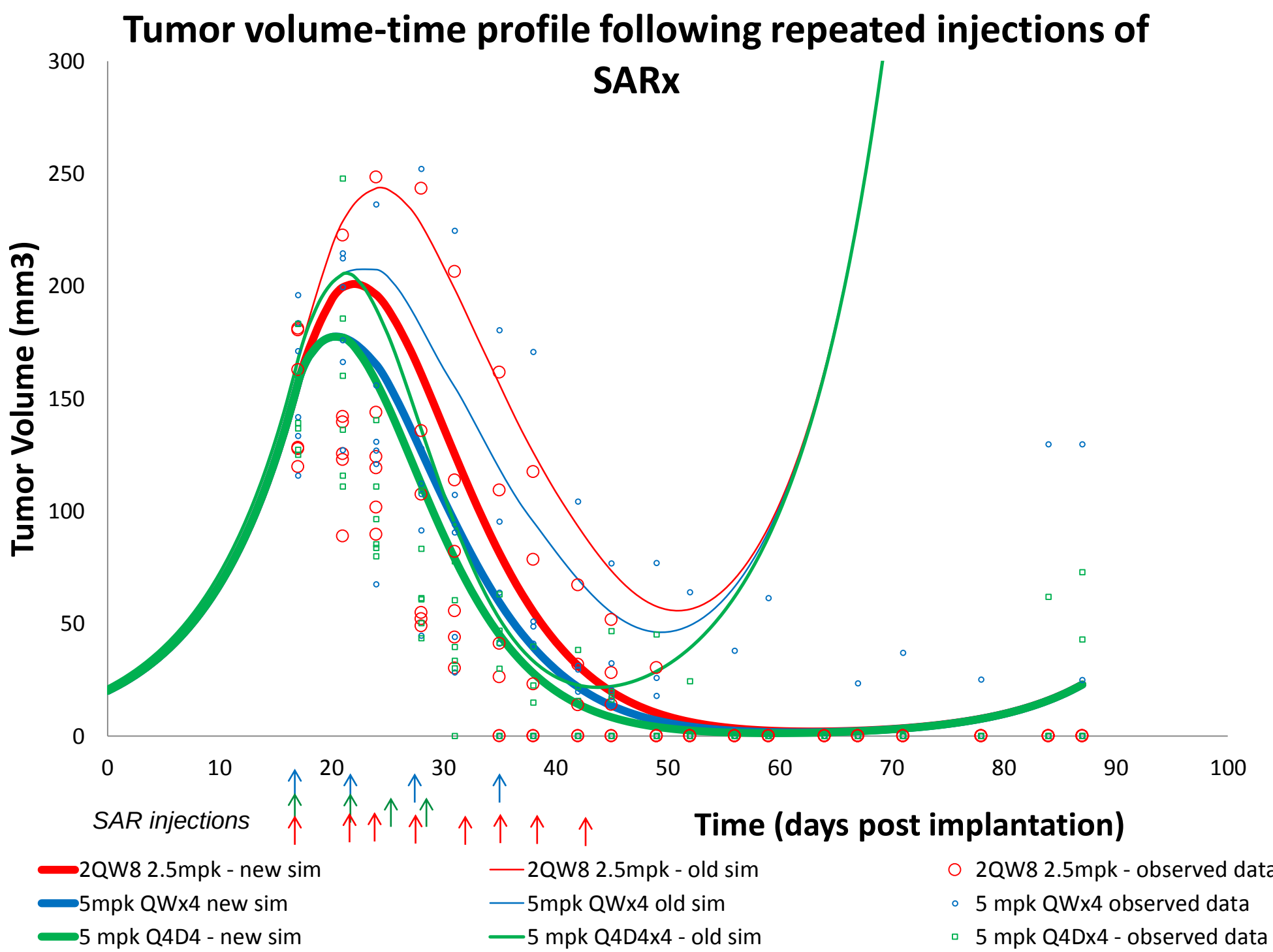
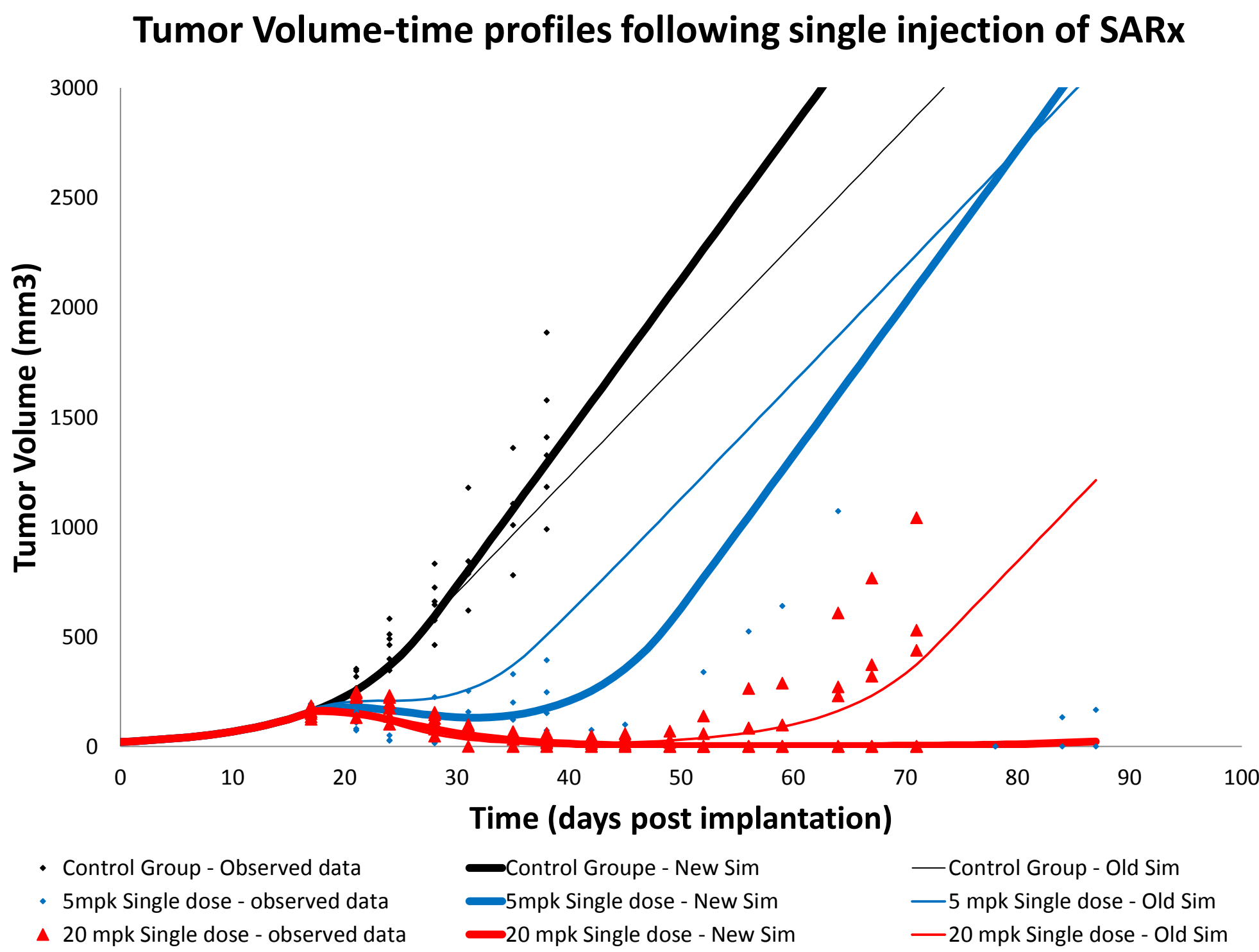
Results

1) Population PK modeling in mice:

The PK were well described using a two-compartment linear model with a low plasma clearance of 1.02 mL/day corresponding to a terminal half-life of 1.8 days and a low distribution volume at steady-state of 2.5 mL.

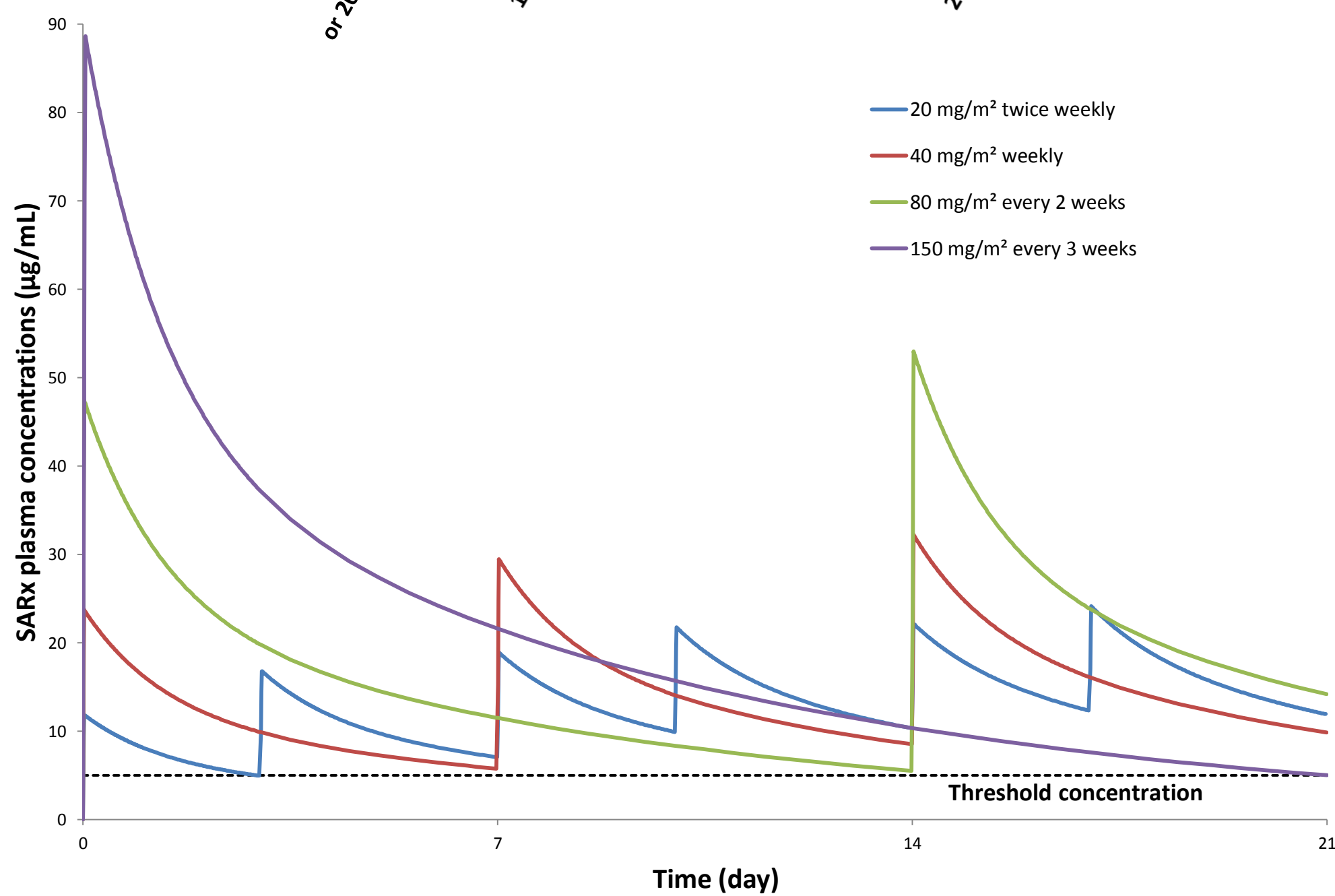
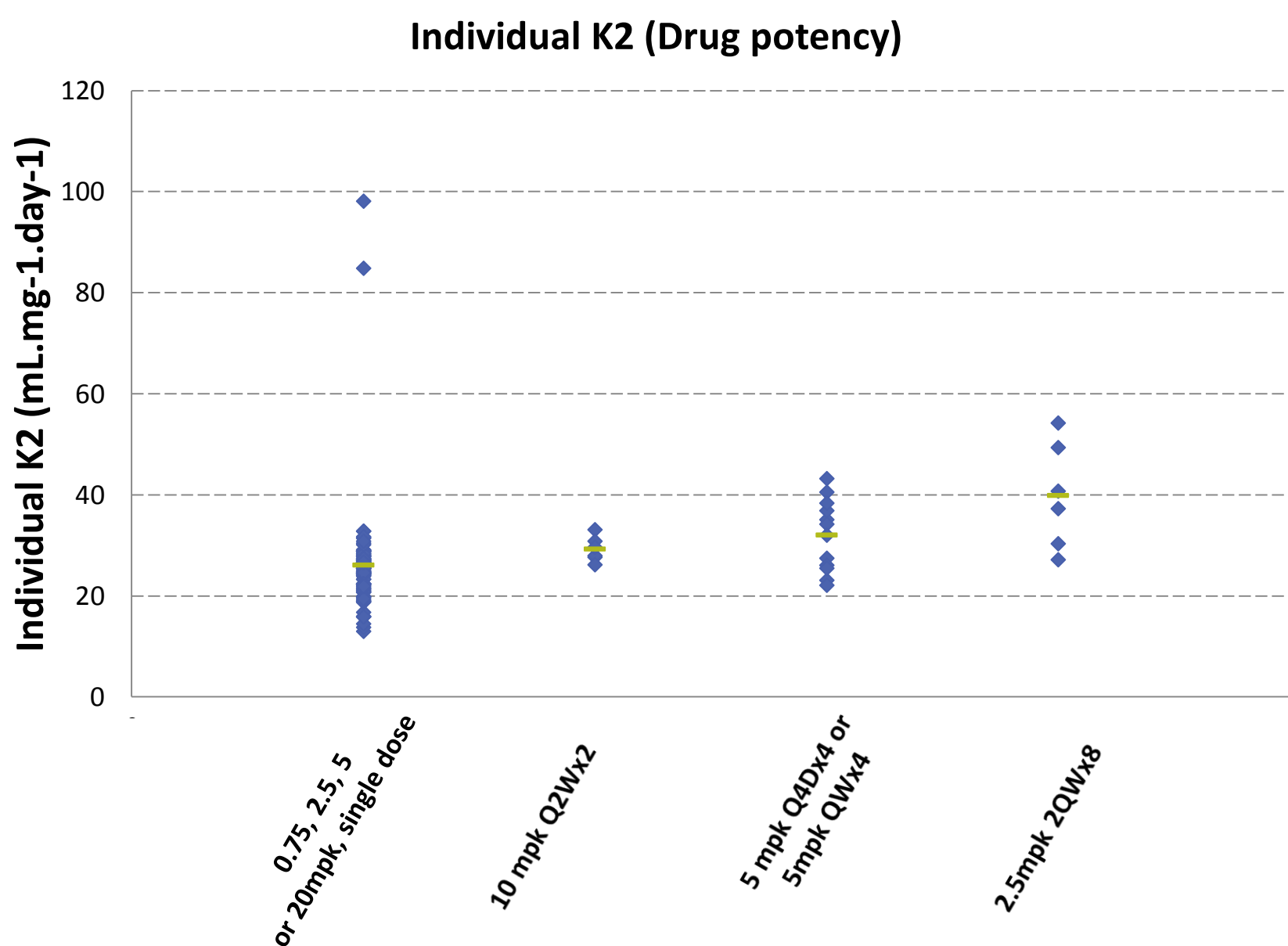
2) Tumor growth modeling (Simeoni) in mice:

The TGI model was found to predict well both single and repeated dose tumor volume data.



Evaluation of K2 and CT

- Individual values of K2 (drug potency) increases with number of intake when the dose is split.
- When repeated dose data are included, the new estimated threshold concentration CT was lower than in the model including only single dose data **8.3 vs 4.6 µg/mL**.



3) Population PK in monkey and clinical translation

- A simple allometric equation ($CL_{human} = CL_{monkey} * [BW_{human} / BW_{monkey}]^\alpha$) with exponent $\alpha=1$ was applied to perform simulations in human ⁽¹⁾ (more conservative approach for efficacy - higher clearance).
- Predicted PK parameters in human : $CL=24.3$ mL/h, $V1= 3.17$ L, $Q=32.7$ mL/h and $V2=1.87$ L.
- Active dosing regimens should maintain plasma concentration above the threshold concentration for tumor eradication (CT).
- With a q2w regimen, doses below 80 mg/m² are expected to be sub-optimal.
- Dosing regimens to be adapted according to safety.

(1) Haddish-Berhane N. et al. (2013) J Pharmacokinet Pharmacodyn 40(5):557-571.

Conclusions & Critical Impact

- Hypothesis and limitations of the model due to lack of PK data:**
 - No PK data after repeated administrations (stationary assumption)
 - No PK data for doses higher than 5 mg/kg (linearity assumption)
 - Hypothesis and limitations of the model that would impact translatability:**
Considering that CT may vary from one PDX model to another, depending on the expression of the target and sensitivity to the cytotoxic, such a study might be repeated in additional models.
- This translational strategy may be a valuable tool to help designing future clinical studies of ADC compounds and to select the most appropriate dosing regimen for tumor eradication.**